REMARKS

Claims 42, 43, 45, 46, and 47 are pending and all stand currently amended. Claims 52 and 53 have been added. The amendments are fully supported by the claims as filed and no new matter is believed to have been added.

Claims 42 – 43; and 45-47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 - 787).

Claim 45 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ball et al. (WO 95/34578).

Claim 45 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ball et al. (US Patent No. 6,008,340).

Claims 42 – 43; and 45-47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (US Patent No. 6,008,340) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 - 787).

The above amendments and the following remarks have addressed all the grounds for rejection and/or objection or have otherwise rendered them moot. Applicants respectfully request the Examiner reconsider all outstanding rejections, and that they be withdrawn.

Examiner Interview

Applicants gratefully acknowledge the Examiner's time and attention in the Examiner Interview held on October 08, 2009. The above claims were discussed and the Examiner was of the opinion that the claims appear patentable so long as it is clear that the "two or more different naturally occurring timothy grass pollen allergens" were of the recombinant kind. Applicants believe that the process steps recited in the claims relate to recombinant manufacture of the fusion allergens of the present invention. Accordingly, it is believed that the claims as presented are allowable and Applicants respectfully solicit the Examiner's reconsideration of the claims.

Rejections Under 35 U.S.C. § 103(a)

Claims 42 – 43; and 45-47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 - 787).

Claims 42 – 43; and 45-47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (US Patent No. 6,008,340) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 - 787).

The Examiner established the above rejections in Paragraphs 4 and 9 of the Office Action respectively. US 6,008,340 being a §371 National Phase of WO 95/34578; it is not believed that there is any substantive difference in the teachings of US 6,008,340 and WO 95/34578. Applicants deem the above grounds for rejection as non-differentiable and shall deal with them as such.

The Examiner asserts that Ball et al., teach a timothy grass pollen allergen as a recombinant or synthetic protein or polypeptide comprising Phl p1 to enhance the display of antigenicity (page 3, lines 33-35). The Examiner further asserts that Ball et al. teach that the protein or polypeptide may be fused to an additional polypeptide; both of which are expressed as a fusion protein in prokaryotic or eukaryotic cells (page 4, lines 1-4). The Examiner asserts that Ball et al., teach that the Phl p1 timothy grass pollen allergen is part of a fusion polypeptide. However, the Examiner admits that Ball et al., do not teach fusion proteins consisting of two or more timothy grass pollen allergens.

To cure the deficiency in Ball et al., the Examiner asserts that Vrtala et al. teach that fusion polypeptides do not significantly affect the allergen's IgE-binding capacity (page 782, col. 1). The Examiner further asserts that Vrtala et al. teach the construction of expression plasmids for Phl p1, Phl p2 and Phl p 5. (page 782 col. 1).

The Examiner concludes that it would have been prima facie obvious at the time of applicant's invention to apply Vrtala et al., recombinant Phl p1, Phl p2 and Phl p5 to Ball et al's pharmaceutical composition or hybrid allergen in order to enhance antigenicity. The Examiner

further asserts that Ball et al. teach the desire to effect antigenicity, and the binding of IgE using fusion polypeptides and that no more than routine skill would have been required to make the combination which the Examiner deems obvious since Ball et al. allegedly taught that timothy grass pollen allergens are amenable to being comprised within fusion proteins and/or hybrid polypeptides and are amenable to fusion with any other expressible polypeptide, while Vrtala et al. teach these allegedly same timothy grass pollen allergens are expressible in prokaryotic or eukaryotic cells.

Applicants respectfully differ with both the premises and the conclusions propounded by the Examiner per the teachings of Ball et al. and Vrtala et al. Whether under the TSM or KSR rule, there is no rational basis to make the combination which the Examiner alleges as obvious. Applicants will deal with the Examiner's statements in the below separately numbered paragraphs.

A. Contrary to the Examiner's assertion, Ball et al., do not teach a timothy grass pollen allergen as a recombinant or synthetic protein or polypeptide comprising Phl p1 to enhance the display of antigenicity (page 3, lines 33-35); it teaches the use of nucleotide segments containing strictly **epitopes of Phl p1** such that the inventive protein or polypeptides of the invention are often shorter than 25% of the full length Phl p1 allergen. (See Column 3, lines 7-25).

B. Contrary to the Examiner's assertion that Ball et al. teach that the protein or polypeptide may be fused to an additional polypeptide; both of which are expressed as a fusion protein in prokaryotic or eukaryotic cells (page 4, lines 1-4), Ball et al. never taught nor suggested any more than expressible fusion proteins for enhanced expression of their inventive protein or polypeptide.

The entire teaching of Ball et al. with respect to fusion proteins of Phl pl epitopes and expressible polypeptides is as follows:

A fourth aspect of the invention is a recombinant or synthetic protein or

> polypeptide displaying the antigenicity of a Phl p I epitope, in particular comprising as an essential part a Phl p I epitope of at least one of the sequences set out in SEQ ID NOS: 5, 7 and 9-28. The protein or polypeptides may be fused to an additional polypeptide, such as beta galactosidase, GST or lambda cII protein or **any other polypeptide that can be expressed** as **a fusion protein** in prokaryotic or eukaryotic cells. U.S. 6,008,340 Col. 2, In 64 -67; Col. 3, In 1-6.

Per the above excerpt, Ball et al. teach the expression of Phl pl epitopes fused with expressible proteins in order to amplify the expression of the Phl pl epitope.

C. Assuming for the sake of argument that Ball et al., indeed teach that the Phl p1 timothy grass pollen allergen is part of a fusion polypeptide, there is no teaching nor suggestion in Ball et al that the Phl p1 "fusion protein" comprise another antigenically active protein or polypeptide in addition to those that may be derived from Phl p1.

D. The Examiner's assertion that Vrtala et al. teach that fusion polypeptides do not significantly affect the allergens IgE-bining capacity (page 782, col. 1) is clear and manifest error and is not supported by the plain textual disposition of the cited section which reads as follows:

> In addition, it was demonstrated that recombinant timothy grass pollen allergens bound a high proportion of grass pollen-specific IgE. However, the previous assays were done with **recombinant β-galactosidase fusion allergens**, which in addition to the mature protein contained the leader peptides and a large portion of **β** -galactosidase. Although **the fused polypeptide** did not significantly affect the allergens' IgE binding capacity, the purification protocols had delivered rather small amounts of the recombinant allergens. Page 782 Col 1. Paragraph 1.

The fused polypeptide in the above excerpt refer to the recombinant **β** -galactosidase fusion allergens and does not stand as a general proposition, as the Examiner asserts, that **ALL** fusion polypeptides do not affect an allergens IgE-biding capacity. As an elementary proposition, the physico-chemical properties of fusion proteins should be expected to affect the proteins tertiary structure such that certain epitopic sites may be foldably excluded from IgE binding. The fact

that β -galactosidase does not significantly affect the allergen's IgE binding capacity cannot, with any reasonable degree of scientific certainty, support an assertion that all fusion proteins do not significantly affect the IgE-binding capacity of the constituent allergens.

E. Other than β -galactosidase fusion proteins, Vrtala et al. taught strictly in terms of production of large quantities of non-fused timothy grass pollen allergens. See Page 787, Col. 1, Paragraph 1. See also Abstract page 781.

F. Assuming that Ball et al. and Vrtala et al. are properly combinable; under either the TSM standard or the KSR standard, it remains fundamentally counter intuitive that a fusion of antigenically active polypeptides could have reduced allergenic activity compared with the respective wild-type allergens.

The Examiner's basis for making this combination which she deems obvious is the teaching of expressible fusion proteins containing a timothy grass pollen allergen. In each case, in the cited prior arts, other than the timothy grass pollen allergen, the other constituent of the fusion entity is antigenically non-active. If anything, the combination teaches the fusion of timothy grass pollen allergen with antigenically non-active peptides. In the case of the instant invention, the fusion allergen consists of antigenically active polypeptides which derive their therapeutic benefit on the basis of the instant invention in having reduced allergenic activity compared with the respective wild-type constituents of the fusion allergen.

The rational inquiry under KSR is not whether Ball et al. taught the fusion of timothy grass pollen allergen with an expression booster protein; but whether Ball et al. can rationally stand for any teaching that fused timothy grass pollen allergens can and do have immunotherapeutic benefits. Prior to the current invention, no one has taught nor suggested that the fusion of hybrid allergens each comprising antigenically active segments can produce immunotherapeutic agents more desirable than the respective component allergens. That such is the case was indeed a surprise to the inventors who are leading researchers

in this area, and is in fact a surprise to anyone who is abreast with the developments in this art area. The Rule 132 declaration submitted prior affirmed the inventor's surprise that fusion proteins of naturally occurring allergens can be used as immunotherapeutic agents and exhibit increased immunogenicity. See Rule 132 declaration dated September 28, 2004. That factor of surprise coupled with long felt obvious need to cross-sensitize patients against a broad spectrum of allergens with administration of the least amount of immunotherapeutic agents capable of inducing anaphylactic side effects, all tend to negate a rational underpinning for the use of Ball et al. against the current invention.

It is respectfully requested that the Examiner reconsider and withdraw this ground for rejection.

Rejections Under 35 U.S.C. § 102(b)

Claim 45 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ball et al. (WO 95/34578).

Claim 45 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ball et al. (US Patent No. 6,008,340).

The claims have been amended such that the fusion proteins of the instant invention consists of two or more different naturally occurring timothy grass pollen allergens. As the Examiner readily admitted, Ball et al., do not teach fusion proteins consisting of two or more timothy grass pollen allergens. On the basis of the all elements rule, it is believed that this ground for rejection has been rendered moot and its withdrawal is respectfully requested.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants respectfully request that the Examiner reconsider

all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. Applicants wish to expedite the prosecution process and if the Examiner believes, for any reason that personal communication will help expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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By:_____

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